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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,822	03/23/2005	Aurelio Orjales Venero	P/4043-153	6533

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
07/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,822	ORJALES VENERO ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *25* is/are allowed.

6)☐ Claim(s) *26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment and response filed by applicants dated April 24, 2008 have been entered and considered carefully.

Claims 1-24 are pending. New claims 25-32 are pending.

2. The rejection of claims 1-24 under 35 USC 112 second paragraph is moot in view of their cancellation.

3. The rejection of claims 1-3, 15-18 under 35 USC 112 first paragraph for lacking product with only X-ray or IR is moot in view of their cancellation.

4. The rejections of claims 15-18, or 4-5 and 15-18 under 35 USC 112 first paragraph for lacking enablement are maintained for reason of record for the newly presented claims 26-27 and 31-32.

Please note that the newly presented claims 26-27 is a process of "heating" bilastine in a solvent which does not have any steps of a "procedure". In addition, as evidenced by the state-of-the-art with reference Kirk-Othmer, it was clearly documented that preparation of polymorphic crystalline forms for a given compound is highly unpredictable and specific. Each solvent, temperature and concentration, even the size of the reaction vessel, scratching etc. may be the criticality for obtaining single crystalline form excluding impurity forms.

Applicants argued that examples 1-5 provided "information" on how to pick and choose any "short chain alcohols, acetones or mixture thereof" with choices of temperature, concentration, time, ratio etc. This argument is contradictory with the above state of the art as well as the support of the specification. Please note that examples 1-5 used isopropyl alcohol twice, n-butanol twice, acetone once. Nowhere in the specification any other 'short chain alsohol" or acetone or mixtures were evidenced. In view of the criticality in operation, absent of factual evidence, the argument lacks support from the state of the art or the specification.

5. The rejection of claims 9-14 under 35 USC 112 first paragraph for lacking sufficient enablement in making a pharmaceutical composition maintaining crystalline form I or being able to use crystalline form 1 in obtaining antihisminic or antiallergenic effect is maintained for reason of record and for newly added claims 28-30.

Applicants argued that claims 28-30 now requires X-ray diffraction spectra since they are now dependent on claim 25, therefore:

> *"It is respectfully submitted, however, in response that it would be well known to one having an ordinary degree of skill in this art at the time the present invention was made both that it is important to maintain control of the crystalline form of the bilastine and, in addition, how to maintain such control over the crystalline form. That is to say that both of these issues are well within the province of one having an ordinary level of skill in the subject art and, thus, both steps are capable of being accomplished by such an individual without the need for any undue experimentation".*

This argument is contradictory to the per ponderous evidence made of record in the last office action. Please note that, it was evidenced that the reasonable expectation in pharmaceutical formulation is that "specific crystalline" forms would be changed. It is only by factual measurements of the final tablet or capsule etc. that the maintenance of such form can be made and such maintenance is the result of very particular carrier and processing conditions.

The specification provided description of general processing including liquid and wet granulation for which the crystalline forms are well recognized would be changed. No support can be found to the argument recited supra.

6. The rejections of claims 6-10 under 35 USC 102(b) or 103(a) are maintained for reason of record for newly added claims 28-30.

In response to the scope of liquid composition as described in the specification, applicants argued that:

> *"In response to this rejection, applicants respectfully note that the Orjales et al. reference discloses that bilastine is obtained as a 'crude' product having a melting point range of from 199- 201 °C. The melting point of pure crystalline form 2 is 205.2°C whereas the melting point of pure crystalline form 3 is 197 °C, as taught by applicants (see, e.g., p. 4, lines 10-11). From this it is apparent, therefore, that the crude product disclosed in the reference is comprised of a mixture of crystalline forms 2 and 3 of bilastine. It does not consist of pure crystalline form 2, or pure crystalline form 3 or a mixture of the ~ crystalline forms. In summary, therefore, the histaminic/antiallergenic*

properties produced as described in the Orjales et al. reference are produced by a mixture of crystalline forms 2 and 3, and not by a composition containing the crystalline form 1 ofbilastine as recited in new claims 28 and 29, which have taken the place of original claims 6-10."

Physical characteristics of crystals as recited supra has no meaning to a liquid composition comprising bilastine because the only difference of a liquid is the "concentration" of its active ingredients. Melting points provide no factual support that the concentration of any polymeric forms of biastine would actually be any different. Even if the solubility between polymeric forms are different, the difference in a liquid composition is merely by amount not by kind because the compound in liquid is identical and adjustment of concentration is by using more or less solvent. Solubility information, especially dissolution rate, can affect efficacy but such difference has not been evidenced between the instant form and the prior art form.

In response to the solid composition, applicants argued that:

"... taking into account the Examiner's point that a solid will loose its crystalline structure when it is solvated by a solvent, applicants respectfully submit that new claims 28-29 as now formulated recite a pharmaceutical preparation and a method for making the same wherein the active ingredient (i.e., the crystalline form 1 of bilastine) is not solvated but, rather, is in a solid form. Support for the claims to these embodiments is found at pps. 8-10 of applicants' specification, which separately describes solid and liquid preparations. In light of the Examiner's remarks, therefore, applicants' have elected to limit their claims to the pharmaceutical preparation and the method of making the same to the solid form of the preparation while excluding 'solutions', i.e., wherein the crystalline form becomes solvated."

One can claim and use the solid composition comprising a "form with X-ray..." when one is in possession of such a composition. The discussion of section 5 supra is also applicable here and incorporated by reference. As evidence by per ponderous of evidence in the state of the art, polymeric forms upon compressing would change into the thermodynamically most stable form due to such high pressure and energy during compression. Absent of specific carrier for which a "form" can be maintained, all polymeric forms prior art or instant are expected to become the *same identical* composition comprising the most thermal dynamically stable form.

The specification provided description of general processing including liquid and wet granulation for which the crystalline forms are well recognized would be changed. No support such specific carrier or post tableting physical data, can be found to the argument recited supra.

Mere argument lacks support in rebutting the per ponderous of evidence provided in the state of the art.

ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from

7. Claim 25 is allowed.

8. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
July 17, 2008

/Celia Chang/
Primary Examiner
Art Unit 1625